

Optimization of Immunosuppressive Therapy for Spinal Grafting of Human Spinal Stem Cells in a Rat Model of ALS.

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Public Summary:

Scientific Abstract:

Previous rodent studies employing monotherapy or combined immunosuppressive regimens have demonstrated a variable degree of spinal xenograft survival in several spinal neurodegenerative models including spinal ischemia, trauma, or amyotrophic lateral sclerosis (ALS). Accordingly, the characterization of optimal immunosuppressive protocols for the specific neurodegenerative model is critical to ensure reliable assessment of potential long-term therapeutic effects associated with cell replacement. In the present study we characterized the survival of human spinal stem cells when grafted into the lumbar spinal cords of a rodent model of ALS, SOD1 (G93A) male and female rats (60-67 days old). Four different immunosuppressive protocols were studied: i) FK506 (q12h); ii) FK506 (qd) + mycophenolate (PO; q12h, up to 7 days postop); iii) FK506 (qd) + mycophenolate (IP; q12h, up to 7 days postop); and iv) FK506 (qd) + mycophenolate (IP; qd, up to 7 days postop). Three weeks after cell grafting the number of surviving human cells was then systematically assessed. The highest density of grafted cells was seen in animals treated with FK506 (qd) and mycophenolate (IP; qd; an average 915 +/- 95 grafted cells per spinal cord section). The majority of hNUMA-positive cells colocalized with doublecortin (DCX) immunoreactivity. DCX-positive neurons showed extensive axodendritic sprouting toward surrounding host neurons. In addition, migrating grafted cells were identified up to 500 µm from the graft. In animals treated with FK506 (q12h), FK506 (qd) + mycophenolate (PO; q12h) or FK506 (qd) + mycophenolate (IP; q12h), 11.8 +/- 3.4%, 61.2 +/- 7.8%, and 99.4 +/- 8.9% [expressed as percent of the FK506 (qd) and mycophenolate (IP; qd)] cell survival was seen, respectively. In contrast to animals treated with a combination of FK506 + mycophenolate, robust CD4/8 immunoreactivity was identified in the vicinity of the injection tract in animals treated with FK506 only. These data suggest that a combined, systemically delivered immunosuppression regimen including FK506 and mycophenolate can significantly improve survival of human spinal stem cells after intraspinal transplantation in SOD1 (G93A) rats.

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